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Novel Approaches of Floating Drug Delivery System: A Review

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ABSTRACT

Several approaches are currently utilized in the prolongation of the GRT, including floating drug delivery systems (FDDS), swelling and expanding systems, polymeric bioadhesive systems, high-density systems, modified-shape systems and other delayed gastric emptying devices. In this review, current & recent developments of Stomach Specific FDDS are discussed. Drugs with narrow absorption window in the gastrointestinal tract have poor absorption. Therefore, gastroretentive drug delivery systems (GRDDS) have been developed, which prolong the gastric emptying time. Several techniques such as floating drug delivery system, low density systems, raft systems, mucoadhesive systems, high density systems, superporous hydrogels and magnetic systems, have been employed. This review also summarizes the in vitro techniques, in vivo studies to evaluate the performance and application of floating systems, and applications of these systems. The purpose of writing this review on floating drug delivery systems (FDDS) was to compile the recent literature with special focus on the principal mechanism of floatation to achieve gastric retention.

KEYWORDS

Floating drug delivery systems, gastrointestinal tract, mucoadhesive systems

INTRODUCTION

The most important objectives of these new drug delivery systems are: First, it would be single dose, which releases the active ingredient over an extended period of time. Second, it should deliver the active entity directly to the site of action, thus, minimizing or eliminating side effects. To overcome the limitations of conventional drug delivery system, floating tablets have been developed. Drugs that have narrow absorption window in gastrointestinal tract (GIT) will have poor absorption. For these drugs, gastroretentive drug delivery systems offer the advantages in prolonging the gastric emptying time. To formulate a successful stomach specific or gastroretentive drug delivery system, several techniques are currently used such as hydrodynamically balanced systems (HBS) / floating drug delivery system[1]. It has been frequently observed that the drugs that are easily absorbed from GI tract have short half-lives and are eliminated quickly from the systemic circulation which leads to incomplete absorption of drugs from the upper part of the small intestine. The recurrent dosing of the drugs is obligatory to achieve appropriate therapeutic activity and to avoid this limitation, the development of oral sustained- controlled release formulations is an attempt to release the drug slowly into the GI tract that helps to maintain an effective drug concentration in the systemic circulation for a prolonged period of time[2,3] Controlled-release drug delivery system is capable of achieving the benefits like maintenance of optimum therapeutic drug concentration in blood with predictable and reproducible release rates for extended time

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period; enhancement of activity of duration for short half-life drugs; elimination of side effects; reducing frequency of dosing and wastage of drugs; optimized therapy and better patient compliances[4,5]. The successful development of oral controlled drug delivery systems requires an understanding of the three aspects of the system, namely.

1. The physiochemical characteristics of the drug

2. Anatomy and physiology of GIT and Characteristics of Dosage Forms[6]

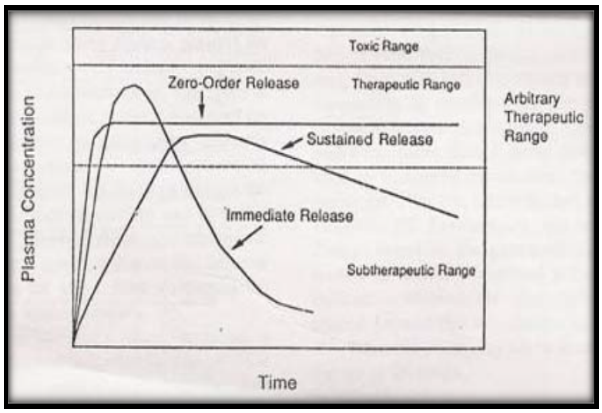

Figure 1: Drug level verses time profile showing differences between zero order, controlled releases, slow first order sustained release and release from conventional tablet

Floating Drug Delivery Systems and its Mechanism

Floating drug delivery systems (FDDS) have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach. This results in an increased GRT and a better control of the fluctuations in plasma drug concentration. However, besides a minimal gastric content needed to allow the proper achievement of the buoyancy retention principle, a minimal level of floating force (F) is also required to keep the dosage form reliably buoyant on the surface of the meal. To measure the floating force kinetics, a novel apparatus for determination of resultant weight has been reported in the literature. The apparatus operates by measuring continuously the force equivalent to F (as a function of time) that is required to maintain the submerged object. The object floats better if F is on the higher positive side (Figure 1(b)). This apparatus helps in optimizing FDDS with respect to stability and durability of floating forces produced in order to

Conventional V/S Gastroretentive Drug Delivery System

Sr. No.	Convention	Gastro retentive drug
1	High risk of toxicity	Very low risk of toxicity
2	Less patient compliance	Improves patient compliance
3	Not suitable for delivery of drugs with narrow absorption window in small intestine region.	Suitable for delivery of drugs with narrow absorption window in small intestine region
4	Not much advantageous for Drugs having rapid absorption through GIT	Very much advantageous for Drugs acting locally in the stomach
5	Drugs which are poorly soluble at an alkaline pH	Drugs having rapid absorption through GIT
6	No risk of dose dumping.	Possibility of dose dumping

prevent the drawbacks of unforeseeable intragastric buoyancy capability variations[7]

F = F buoyancy - F gravity

= (Df - Ds) gv ---------- (1)

Where, F= total vertical force,

Df = fluid density,

Ds = object density,

v = volume and g=acceleration due to gravity.

amount of drug (>50%) and achieve required density of 2.4-2.8g/cm3. Diluents such as barium sulphate (density= 4.9), zinc oxide, titanium oxide, and iron powder must be used to manufacture such high-density formulation[8].

Swelling and Expanding Systems

These systems are also called as "Plug type system", since they exhibit tendency to remain logged in the pyloric sphincters. These polymeric matrices remain in the gastric cavity for several hours even in fed state[12].

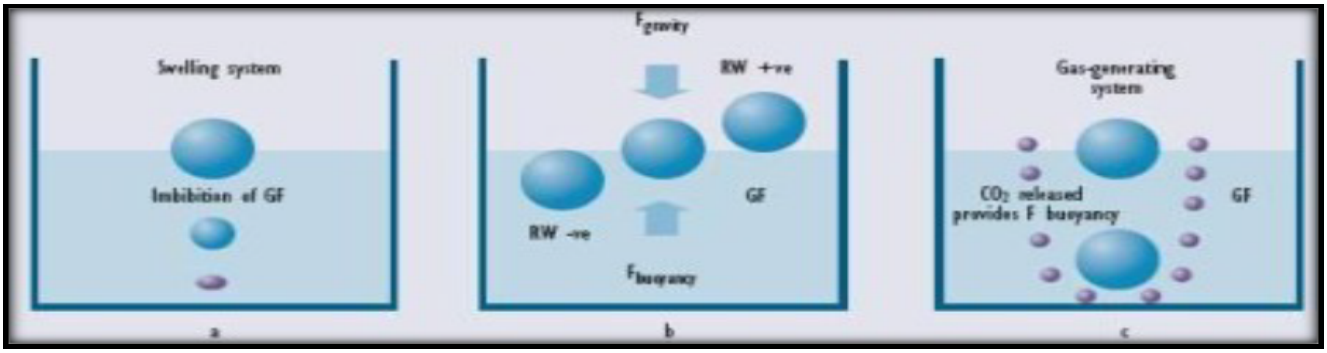

Figure 2: The Mechanism of Floating Systems

Approaches to Gastroretention

Several techniques are reported in the literature to increase the gastric retention of drugs [8-11]

High Density Systems

These systems, which have a density of ~3g/cm3, are retained in the rogue of stomach and capable of withstanding its peristaltic movements18, 20. The only major drawback with these systems is that it is technically difficult to manufacture them with a large

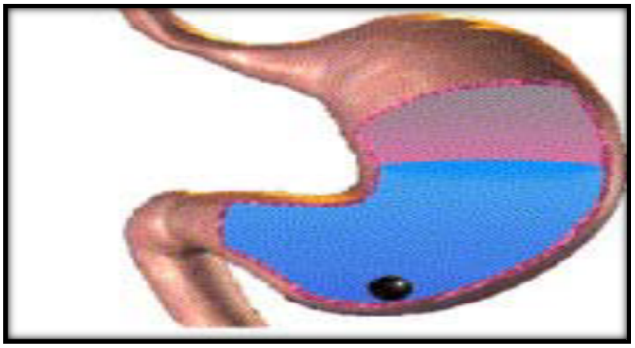

Figure 3: Swellable Tablet in Stomach

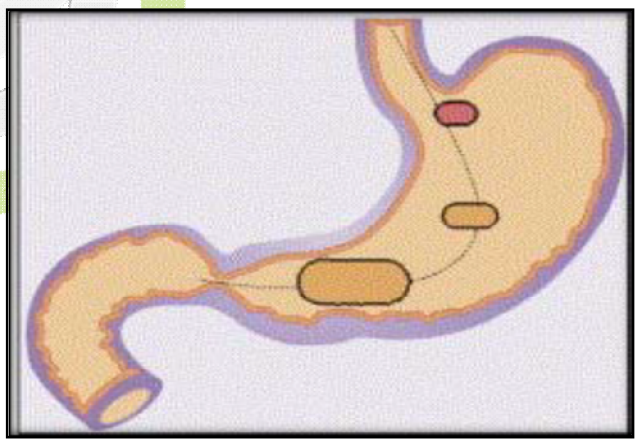

Figure 4: Swellable Tablet in Stomach

By selection of polymer with the proper molecular weight and swelling properties controlled and sustained drug release can be achieved. Upon coming in contact with gastric fluid, the polymer imbibes water and swells. The extensive swelling of these polymersis a result of the presence of physical-chemical cross links in the hydrophilic polymer network. These cross link prevents the dissolution of polymer and thus maintain the physical integrity of the

dosage form. A high degree of cross linking retards the swelling ability of the system and maintains its physical integrity for prolonged period. On the other hand, a low degree of cross linking results in extensive swelling followed by the rapid dissolution of polymer[13].

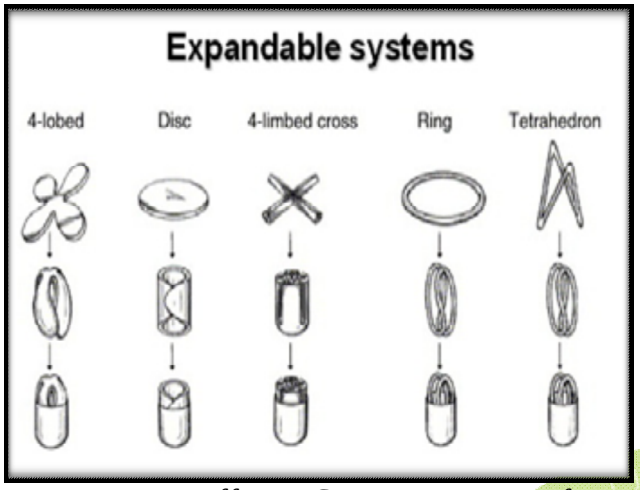

Figure 5: Different Geometric Forms of Unfoldable Systems

Incorporating Delaying Excipients

Another delayed gastric emptying approach of interest include feeding of digestible polymers or fatty acid salts that charges the motility pattern, of the stomach to a fed stage thereby decreasing the gastric emptying rate and permitting considerable prolongation of the drug release. Prolongation of GRT of drug delivery system consists of incorporating delaying excipients like trietanolamine myristate in a delivery system[14].

Modified Systems

Systems with non-disintegrating geometric shape moulded from silastic elastomers or extruded from polyethylene blends, which extend the GRT depending on size, shape and flexural modules of drug delivery device[15].

Mucoadhesive & Bioadhesive Systems

Bioadhesive drug delivery systems are used to localize a delivery device within the lumen to enhance the drug absorption in a sitespecific manner. This approach involves the use of bioadhesive polymers, which can adhere to the epithelial surface in the stomach. Some of the most promising excipients that have been used commonly in these systems include polycarbophil, carbopol, lectins, chitosan, CMC and gliadin, etc[16,17].

Floating Systems

Floating drug delivery systems (FDDS) have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach[18]. Floatation of a drug delivery system in the stomach can be achieved by incorporating floating chamber filled with vacuum, air, or inert gas.

Factors Affecting Gastric Residence Time of FDDS

a) Formulation Factors

Size of Tablets

Retention of floating dosage forms in stomach depends on the size of tablets. Small tablets are emptied from the stomach during the digestive phase, but large ones are expelled during the house keeping waves[19]. Floating and nonfloating capsules of 3 different sizes having a diameter of 4.8 mm (small units), 7.5 mm (medium units), and 9.9 mm (large units), were formulated and analyzed for their different properties. It was found that floating dosage units remained buoyant regardless of their sizes on the gastric contents throughout their residence in the gastrointestinal tract, while the nonfloating dosage units sank and remained in the lower part of the stomach. Floating units away from the gastro-duodenal junction were protected from the peristaltic waves during digestive phase while the nonfloating forms stayed close to the pylorus and were subjected to propelling and retropelling waves of the digestive phase[20].

Density of Tablets

Density is the main factor affecting the gastric residence time of dosage form. A buoyant

dosage form having a density less than that of the gastric fluids floats, since it is away from the pyloric sphincter, the dosage unit is retained in the stomach for a prolonged period. A density of less than 1.0g/ml i.e. less than that of gastric contents has been reported. However, the floating force kinetics of such dosage form has shown that the bulk density of a dosage form is not the most appropriate parameter for describing its buoyancy capabilities[21].

Shape of Tablets

The shape of dosage form is one of the factors that affect its gastric residence time. Six shapes (ring tetrahedron, cloverleaf, string, pellet, and disk) were screened *in vivo* for their gastric retention potential. The tetrahedron (each leg 2cm long) rings (3.6 cm in diameter) exhibited nearly 100% retention at 24 hr[22].

Viscosity Grade of Polymer

Drug release and floating properties of FDDS are greatly affected by viscosity of polymers and their interaction. Low viscosity polymers (e.g., HPMC K100 LV) were found to be more beneficial than high viscosity polymers (e.g., HPMC K4M) in improving floating properties. In addition, a decrease in the release rate was observed with an increase in polymer viscosity[23].

b) Idiosyncratic Factors

Gender

Women have slower gastric emptying time than do men. Mean ambulatory GRT in meals (3.4±0.4 hours) is less compared with their age and race-matched female counterparts (4.6±1.2 hours), regardless of the weight, height and body surface[24].

Age

Low gastric emptying time is observed in elderly than do in younger subjects. Intrasubject and intersubject variations also are observed in gastric and intestinal transit time. Elderly people, especially those over 70 years have a significantly longer GRT[24].

Posture

i) Upright Position

An upright position protects floating forms against postprandial emptying because the floating form remains above the gastric contents irrespective of its size14. Floating dosage forms show prolonged and more reproducible GRTs while the conventional dosage form sink to the lower part of the distal stomach from where they are expelled through the pylorus by astral peristaltic movements[25].

ii) Supine Position

This position offers no reliable protection against early and erratic emptying. In supine subjects large dosage forms (both conventional and floating) experience prolonged retention. The gastric retention of floating forms appear to remain buoyant anywhere between the lesser and greater curvature of the stomach. On moving distally, these units may be swept away by the peristaltic movements that propel the gastric contents towards the pylorus, leading to significant reduction in GRT compared with upright subjects[26].

Concomitant Intake of Drugs

Drugs such as prokinetic agents (e.g., metoclopramide and cisapride), anti Cholinergics (e.g., atropine or propantheline), opiates (e.g., codeine) may affect the performance of FDDS. The coadministration of GI-motility decreasing drugs can increase gastric emptying time[26].

Feeding Regimen

Gastric residence time increases in the presence of food, leading to increased drug dissolution of the dosage form at the most favourable site of absorption. A GRT of 4-10 h has been reported after a meal of fats and proteins[26.]

Classification of Floating Drug Delivery Systems (FDDS)

Floating drug delivery systems are classified depending on the use of 2 formulation variables: effervescent and noneffervescent systems.

Effervescent Floating Dosage Forms

These are matrix types of systems prepared with the help of swellable polymers such as methylcellulose and chitosan and various effervescent compounds, eg, sodium bicarbonate, tartaric acid, and citric acid. They are formulated in such a way that when in contact with the acidic gastric contents, CO2 is liberated and gets entrapped in swollen hydrocolloids, which provides buoyancy to the dosage forms.

Ichikawa et al[27] developed a new multiple type of floating dosage system composed of effervescent layers and swellable membrane layers coated on sustained release pills. The inner layer of effervescent agents containing sodium bicarbonate and tartaric acid was divided into 2 sublayers to avoid direct contact between the 2 agents. These sublayers were surrounded by a swellable polymer membrane containing polyvinyl acetate and purified shellac. When this system was immersed in the buffer at 37ºC, it settled down and the solution permeated into the effervescent layer through the outer swellable membrane. CO2 was generated by the neutralization reaction between the 2 effervescent agents, producing swollen pills (like balloons) with a density less than 1.0 g/mL. It was found that the system had good floating ability independent of pH and viscosity and the drug (para-amino benzoic acid) released in a sustained manner28 (Figure 2, A and B).

Ichikawa et al[28] developed floating capsules composed of a plurality of granules that have different residence times in the stomach and consist of an inner foamable layer of gasgenerating agents. This layer was further divided into 2 sublayers, the outer containing sodium bicarbonate and the inner containing tartaric acid. This layer was surrounded by an expansive polymeric film (composed of poly vinyl acetate [PVA] and shellac), which allowed gastric juice to pass through, and was found to swell by foam produced by the action between the gastric juices and the gas-generating agents.29 It was shown that the swellable membrane layer played an important role in maintaining the buoyancy of the pills for an extended period of time. Two parameters were evaluated: the time for the pills to be floating (TPF) and rate of pills floating at 5 hours (FP5h). It was observed that both the TPF and FP5h increased as the percentage of swellable membrane layer coated on pills having a effervescent layer increased. As the percentage of swellable layer was increased from 13% to 25% (wt/wt), the release rate was decreased and the lag time for dissolution also increased. The percentage of swellable layer was fixed at 13% wt/wt and the optimized system showed excellent floating ability in vitro (TPF ~10 minutes and FP5h ~80%) independent of pH and viscosity of the medium.

Yang et al[29] developed a swellable asymmetric triple-layer tablet with floating ability to prolong the gastric residence time of triple drug regimen (tetracycline, metronidazole, and clarithromycin) in Helicobacter pylori–associated peptic ulcers using hydroxy propyl methyl cellulose (HPMC) and poly (ethylene oxide) (PEO) as the rate-controlling polymeric membrane excipients. The design of the delivery system was based on the swellable asymmetric triple-layer tablet approach. Hydroxypropylmethylcellulose and poly (ethylene oxide) were the major rate-controlling polymeric excipients. Tetracycline and metronidazole were incorporated into the core layer of the triple-layer matrix for controlled delivery, while bismuth salt was included in one of the outer layers for instant release. The floatation was accomplished by incorporating gas-generating layer consisting of sodium bicarbonate: calcium carbonate (1:2 ratios) along with the polymers. The in vitro results revealed that the sustained delivery of tetracycline and metronidazole over 6 to 8 hours could be achieved while the tablet remained afloat. The floating feature aided in prolonging the gastric residence time of this system to maintain high localized concentration of tetracycline and metronidazole Oz emir

Yang et al [30] developed floating bilayer tablets with controlled release for furosemide. The low solubility of the drug could be enhanced by

using the kneading method, preparing a solid dispersion with β cyclodextrin mixed in a 1:1 ratio. One layer contained the polymers HPMC 4000, HPMC 100, and CMC (for the control of the drug delivery) and the drug. The second layer contained the effervescent mixture of sodium bicarbonate and citric acid. The in vitro floating studies revealed that the lesser the compression force the shorter is the time of onset of floating, ie, when the tablets were compressed at 15 MPa, these could begin to float at 20 minutes whereas at a force of 32 MPa the time was prolonged to 45 minutes. Radiographic studies on 6 healthy male volunteers revealed that floating tablets were retained in stomach for 6 hours and further blood analysis studies showed that bioavailability of these tablets was1.8 times that of the conventional tablets. On measuring the volume of urine the peak diuretic effect seen in the conventional tablets was decreased and prolonged in the case of floating dosage form.

Choi et al[31] prepared floating alginate beads using gasforming agents (calcium carbonate and sodium bicarbonate) and studied the effect of CO2 generation on the physical properties, morphology, and release rates. The study revealed that the kind and amount of gas-forming agent had a profound effect on the size, floating ability, pore structure, morphology, release rate, and mechanical strength of the floating beads. It was concluded that calcium carbonate formed smaller but stronger beads than sodium bicarbonate. Calcium carbonate was shown to be a less-effective gas forming agent than sodium bicarbonate but it produced superior floating beads with enhanced control of drug release rates.

Baumgartner et al[32] developed a matrix-floating tablet incorporating a high dose of freely soluble drug. The formulation containing 54.7% of drug, HPMC K4 M, Avicel PH 101, and a gas-generating agent gave the best results. It took 30 seconds to become buoyant. In vivo experiments with fasted state beagle dogs revealed prolonged gastric residence time. On radiographic images made after 30 minutes of administration, the tablet was observed in animal's stomach and the next image taken at 1 hour showed that the tablet altered its position and turned around. This was the evidence that the tablet did not adhere to the gastric mucosa. The MMC (phase during which large no disintegrating particles or dosage forms are emptied from stomach to small intestine) of the gastric emptying cycle occurs approximately every 2 hours in humans and every 1 hour in dogs but the results showed that the mean gastric residence time of the tablets was 240 ± 60 minutes (n = 4) in dogs. The comparison of gastric motility and stomach emptying between humans and dogs showed no big difference and therefore it was speculated that the experimentally proven increased gastric residence time in beagle dogs could be compared with known literature for humans, where this time is less than 2 hours.

Non-Effervescent Floating Dosage Forms

Non-effervescent floating dosage forms use a gel forming or swellable cellulose type of hydrocolloids, polysaccharides, and matrix-forming polymers like polycarbonate, polyacrylate, polymethacrylate, and polystyrene. The formulation method includes a simple approach of thoroughly mixing the drug and the gel-forming hydrocolloid. After oral administration this dosage form swells in contact with gastric fluids and attains a bulk density of G 1. The air entrapped within the swollen matrix imparts buoyancy to the dosage form. The so formed swollen gel-like structure acts as a reservoir and allows sustained release of drug through the gelatinous mass.

Thanoz et al[33] developed polycarbonate microspheres by solvent evaporation technique. Polycarbonate in dichloromethane was found to give hollow microspheres that floated on water and simulated biofluids as evidenced by scanning electron microscopy (SEM). High drug loading was achieved and drug-loaded microspheres were able to float on gastric and intestinal fluids. It was found that increasing the drug to polymer ratio increased both their mean particle size and release rate of drug.

Nur and Zhang et al[34] developed floating tablets of captopril using HPMC (4000 and 15 000 cps) and carbopol 934P. In vitro buoyancy studies revealed that tablets of 2 kg/cm2 hardness after immersion into the floating media floated immediately and tablets with hardness 4 kg/cm2 sank for 3 to 4 minutes and then came to the surface. Tablets in both cases remained floating for 24 hours. The tablet with 8 kg/cm2 hardness showed no floating capability. It was concluded that the buoyancy of the tablet is governed by both the swelling of the hydrocolloid particles on the tablet surface when it contacts the gastric fluids and the presence of internal voids in the centre of the tablet (porosity). A prolonged release from these floating tablets was observed as compared with the conventional tablets and a 24-hour controlled release from the dosage form of captopril was achieved.

Streubel et al[35] prepared single-unit floating tablets based on polypropylene foam powder and matrix-forming polymer. Incorporation of highly porous foam powder in matrix tablets provided density much lower than the density of the release medium. A 17% wt/wt foam powder (based on mass of tablet) was achieved in vitro for at least 8 hours. It was concluded that varying the ratios of matrix-forming polymers and the foam powder could alter the drug release patterns effectively. Streubel et al51 developed floating microparticles composed of polypropylene foam, Eudragit S, ethyl cellulose (EC), and polymethyl metha acrylate (PMMA) and were prepared by solvent evaporation technique. High encapsulation efficiencies were observed and were independent of the theoretical drug loading. Good floating behavior was observed as more than 83% of microparticles were floating for at least 8 hours. The in vitro drug release was dependent upon the type of polymer used. At similar drug loading the release rates increased in the following order PMMA G EC G Eudragit S. This could be attributed to the different permeabilities of the drug in these polymers and the drug distribution within the system. Sheth and Tossounian26 developed an HBS system containing a homogeneous mixture of drug and the hydrocolloid in a capsule, which upon contact with gastric fluid acquired and maintained a bulk density of less than 1 thereby being buoyant on the gastric contents of stomach until all the drug was released (Figure 5). Sheth and Tossounian52 developed hydro dynamically balanced sustained release tablets containing drug and hydrophilic hydrocolloids, which on contact with gastric fluids at body temperature formed a soft gelatinous mass on the surface of the tablet and provided a water-impermeable colloid gel barrier on the surface of the tablets. The drug slowly released from the surface of the gelatinous mass that remained buoyant on gastric fluids (Figure 6, A and B). Ushomaru et al53 developed sustained release composition for a capsule containing mixture of cellulose derivative or a starch derivative that formed a gel in water and higher fatty acid glyceride and/or higher alcohol, which was solid at room temperature. The capsules were filled with the above mixture and heated to a temperature above the melting point of the fat components and then cooled and solidified. Bolton and Desai54 developed a noncompressed sustained release tablet that remained afloat on gastric fluids. The tablet formulation comprised 75% of drug and 2% to 6.5%

Asmussen et al[36] invented a device for the controlled release of active compounds in the gastrointestinal tract with delayed pyloric passage, which expanded in contact with gastric fluids and the active agent was released from a multiparticulate preparation. It was claimed that the release of the active compound was better controlled when compared with conventional dosage forms with delayed pyloric passage.

Evaluation of Floating Drug Delivery System

Evaluation of Powder Blend for

a) Angle of Repose

b) Bulk Density

c) Percentage porosity

Evaluation of Tablets for

a) Buoyancy capabilities

b) *In vitro* floating and dissolution behaviour

c) Weight variation

d) Hardness & friability

e) Particle size analysis, surface characterization (for floating microspheres and beads):

f) X-Ray/Gamma Scintigraphy

g) Pharmacokinetic study

Evaluation of Powder Blend[37]

a) Angle of Repose

Angle of repose is defined as "the maximum angle possible between the surface of the pile of powder and the horizontal plane." Lower the angle of repose, better the flow properties. The angle of repose may be calculated by measuring the height (h) of the pile and the radius of the base(r) with ruler.

$$\tan \theta = h/r \qquad \text{……(1)}$$

b) Bulk Density

Bulk density denotes the total density of the material. It includes the true volume of interparticle spaces and intraparticle pores. The packing of particles is mainly responsible for bulk.

Bulk density is defined as:

$$\text{Bulk density} = \frac{\text{Weight of the powder}}{\text{Bulk volume of powder}} \qquad \text{……(2)}$$

When particles are packed, it is possible that a large amount of gaps may be present between the particles. Therefore, trapping of powder allows the particles to shift and remove the voids to minimum volume. The volume occupied by the powder in this condition represents the bulk volume. Substituting this volume for a given weight of powder in equation (2) gives the bulk density.

c) Percentage Porosity

Whether the powder is porous or nonporous, the total porosity expression for the calculation remains the same. Porosity provides information about hardness, disintegration, total porosity etc.

$$\%\ \text{porosity}, € = \frac{\text{void volume} \times 100}{\text{Bulk volume}}$$

$$\%\ \text{porosity}, € = \frac{(\text{bulk volume} - \text{true volume}) \times 100}{\text{True density}}$$

Evaluation of Floating Tablets

Measurement of Buoyancy Capabilities of the FDDS

The floating behaviour is evaluated with resultant weight measurements. The experiment is carried out in two different media, deionised water and simulated meal. The results showed that higher molecular weight polymers with slower rate of hydration had enhanced floating behaviour and it was observed more in simulated meal medium compared to deionised water[38].

In Vitro Floating and Dissolution Behavior

The dissolution tests are generally performed on various drugs using USP dissolution apparatus. USP 28 states "the dosage unit is allowed to sink to the bottom of the vessel before rotation of the blade is started". A small, loose piece of nonreactive material with not more than a few turns of a wire helix may be attached to the dosage units that would otherwise float. However, standard USP or BP methods have not been shown to be reliable predictors of in vitro performance of floating dosage forms[38].

Pillay *et al* applied a helical wire sinker to the swellable floating system of theophylline, which is sparingly soluble in water and concluded that the swelling of the system was inhibited by the wire helix and the drug release also slowed down. To overcome this limitation, a method was developed in which the floating drug delivery system was fully submerged under a ring or mesh assembly, and an increase in drug release was observed. Also, it was shown that the method was more reproducible and consistent. However, no significant change in

the drug release was observed when the proposed method was applied to a swellable floating system of diltiazem, which is a highly water-soluble drug. It was thus concluded that the drug release from swellable floating systems was dependent upon uninhibited swelling, surface exposure, and the solubility of the drug in water[39].

Weight Variation

In practice, composite samples of tablets (usually 10) are taken and weighed throughout the compression process. The composite weight divided by 10, however provides an average weight but contains a problem of averaged value. To help alleviate this problem,

the United States pharmacopeia (USP) provides limits for the permissible variations in the weights of individual tablets expressed as a percentage of the average weight of the sample. The USP provides the weight variation test by weighing 20 tablets individually, calculating the average weight, and comparing the individual tablet weights to the average. The tablets meet the USP test if no more than 2 tablets are outside the percentage limit, and if no tablet differs by more than 2 times the percentage limit[40].

Hardness & Friability

Hardness is defined as the "force required to break a tablet in diametric compression test." Hardness is hence, also termed as the tablet crushing strength. Some devices which are used to test hardness are Monsanto tester, strong Cobb tester, Pfizer tester, etc. The laboratory friability tester is known as the Roche Friabilator. This consists of a device which subjects a number of tablets to the combined effects of abrasion and shock by utilizing a plastic chamber that revolves at 25 rpm & drop the tablet to a distance of six inches with each revolution. Normally, a pre-weighed tablet sample is placed in the friabilator which is then operated for 100 revolutions. Conventional compressed tablets that lose less than 0.5 to 1.0 % of their weight are generally considered acceptable. Most of the effervescent tablets undergo high friability weight losses, which accounts for the special stack packaging, that may be required for these types of tablets[40].

Particle Size Analysis, Surface Characterization (for floating microspheres and beads)

The particle size and the size distribution of beads or microspheres are determined in the dry state using the optical microscopy method. The external and crosssectional morphology (surface characterization) is done by scanning electron microscope (SEM) [38].

XRay/ Gamma Scintigraphy

X-Ray/Gamma Scintigraphy is a very popular evaluation parameter for floating dosage form nowadays. It helps to locate dosage form in the gastrointestinal tract (GIT), by which one can predict and correlate the gastric emptying time and the passage of dosage form in the GIT. Here the inclusion of a radio-opaque material into a solid dosage form enables it to be visualized by X-rays. Similarly, the inclusion of a γ-emitting radionuclide in a formulation allows indirect external observation using a γ-camera or scintiscanner. In case of γ-scintigraphy, the γ-rays emitted by the radionuclide are focused on a camera, which helps to monitor the location of the dosage form in the GIT[38].

Pharmacokinetic Studies

Pharmacokinetic studies are an integral part of the in vivo studies and several works have been reported on these. Sawicki studied the pharmacokinetics of verapamil, from the floating pellets containing drug, filled into a capsule, and compared with the conventional verapamil tablets of similar dose (40 mg). The tmax and AUC (0- infinity) values (3.75 h and 364.65ng/ml -1h respectively) for floating pellets were comparatively higher than those obtained for the conventional verapamil tablets. (tmax value 1.21 h, and AUC value 224.22 mg/ml-1h) [38].

Suitable Drugs for Gastroretention

Delivery of the Drugs in continuous and controlled manner have a lower level of side

effects and provide their effects without the need for repeated dosing or with a low dosage frequency. Sustained release in the stomach is also useful for therapeutic agents that the stomach does not readily absorb, since sustained release prolongs the contact time of the agent in the stomach or in the upper part of the small intestine, from where absorption occurs and contact time limited. Appropriate candidates for controlled release gastro retentive dosage forms are molecules that have poor colonic absorption but are characterized by better absorption properties at the upper parts of the GIT.

1. Narrow absorption window in GI tract, e.g., riboflavin and Levodopa

2. Basically absorbed from stomach and upper part of GIT, e.g., chlordiazepoxide and cinnarazine.

3. Drugs that disturb normal colonic bacteria, e.g., amoxicillin trihydrate.

4. Locally active in the stomach, e.g., antacids and misoprostol.

5. Drugs that degrade in the colon, e.g., ranitidine HCl and metronidazole

Drugs Available as Floating Drug Delivery System

Tablets

- Atenolol[42]
- Ampicillin[43]
- Flouorouracil[44]
- Ciprofloxacin[45]
- Furosemide[46]
- Acetaminophen[47]
- Captopril[48]

Capsules

- Diazepam[49]
- Furosemide[50]
- Propranalol[51]

Granules

- Cinnarizine[59]
- Diltia-zem [59]
- Prednisolone [59]
- Isosorbide mononitrate[59]
- Isosorbide dinitrate. [59]
- Indomethacin[52]
- Diclofenac Sodium[53]
- Prednisolone[54]

Good Candidates for Gastroretentive Drug Delivery System[41]

S.No.	Drug	Category	Half life	Peak time hrs	Bioavailability
1	Verapamil	calcium channel blocker	6	1-2	20-35%
2	Nifedipine	Calcium channel blocker	2	.5-.2	45-65%
3	Omeprazole	Proton pump inhibitor	1-2	1	35-60%
4	Atenolol	Antihypertesive	4	3	40-50%
5	Propranolol	Antihypertensive	4-5	4	26%
6	Verapamil	Antihypertensive 6	6	1.8	35%
7	Diltiazem	Calcium channel blocker	3-3.4	50min	40%
8	Lidocaine	Local anaesthetic	1.5-2	4	35%
9	Clarithromycin	Antibiotic	3-4	2-2.5	50%
10	.Ramipril	ACE inhibitor	2-4	3-5	28%

Microspheres

- Ibuprofen[55]
- Ketoprofen[56]
- Tranilast[57]
- Terfenadine[58]
- Aspirin[59]
- Griseofulvin[59]
- p-nitroaniline[59]
- Acetylsalicylic acid[59]
- Amox-ycillin trihydrate[59]
- Trani-last[59]
- Theophylline[59]
- Isosorbide di nitrate[59]
- Sotalol[59]
- Isosorbide mononitrate[59]

Films[59]

- P-Aminobenzoic acid
- Cinnarizine
- Pireta-nide
- Prednisolone
- Quinidine gluconate

Powders[59]

- Riboflavin
- Phosphate
- Sotalol
- Theophyl-line

Advantages & Disadvantage of Floating Drug Delivery System [59, 60]

Advantages of Floating Drug Delivery system

1. The gastroretensive systems are advantageous for drugs absorbed through the stomach. E.g. Ferrous salts, antacids.

2. Acidic substances like aspirin cause irritation on the stomach wall when come in contact with it. Hence HBS formulation may be useful for the administration of aspirin and other similar drugs.

3. Administration of prolongs release floating dosage forms, tablet or capsules, will result in dissolution of the drug in the gastric fluid. They dissolve in the gastric fluid would be available for absorption in the small intestine after emptying of the stomach contents. It is therefore expected that a drug will be fully absorbed from floating dosage forms if it remains in the solution form even at the alkaline pH of the intestine.

4. The gastroretensive systems are advantageous for drugs meant for local action in the stomach. e.g. antacids.

5. When there is a vigorous intestinal movement and a short transit time as might occur in certain type of diarrhoea, poor absorption is expected. Under such circumstances it may be advantageous to keep the drug in floating condition in stomach to get a relatively better response

Disadvantages of floating drug delivery system

1. Floating system is not feasible for those drugs that have solubility or stability problem in G.I. tract.

2. These systems require a high level of fluid in the stomach for drug delivery to float and work efficiently-coat, water.

3. The drugs that are significantly absorbed throughout gastrointestinal tract, which undergo significant first pass metabolism, are only desirable candidate.

4. Some drugs present in the floating system causes irritation to gastric mucosa.

Applications of Floating Drug Delivery Systems[61,62,63]

1. Enhanced Bioavailability

The bioavailability of riboflavin CR-GRDF is significantly enhanced in comparison to the administration of non-GRDF CR polymeric formulations. There are several different processes, related to absorption and transit of the drug in the gastrointestinal tract, that act concomitantly to influence the magnitude of drug absorption.

2. Sustained Drug Delivery

Oral CR formulations are encountered with problems such as gastric residence time in the GIT. These prob-lems can be overcome with the

HBS systems which can remain in the stomach for long periods and have a bulk density <1 as a result of which they can float on the gastric contents. These systems are relatively larger in size and passing from the pyloric opening is prohibited.

3. Site –specific Drug Delivery Systems

These systems are particularly advantageous for drugs that are specifically absorbed from the stomach or the proximal part of the small intestine .The controlled, slow delivery of drug to the stomach provides sufficient local therapeutic levels and limits the systemic exposure to the drug. This reduces side effects that are caused by the drug in the blood circulation. In addition, the prolonged gastric availability from a site directed delivery system may also reduce the dosing frequency. Eg: Furosemide and Riboflavin.

4. Absorption Enhancement

Drugs which are having poor bioavailability because of site specific absorption from the upper part of the GIT are potential candidates to be formulated as floating drug delivery systems, there by maximizing their absorption.

5. Minimized Adverse Activity at the Colon

Retention of the drug in the HBS systems at the stomach minimizes the amount of drug that reaches the colon. Thus, undesirable activities of the drug in colon may be prevented. This Pharmacodynamics aspect provides the rationale for GRDF formulation for beta lactam antibiotics that are absorbed only from the small intestine, and whose presence in the colon leads to the development of microorganism's resistance.

6. Reduced Fluctuations of Drug Concentration

Continuous input of the drug following CRGRDF administration produces blood drug concentrations within a narrower range compared to the immediate release dosage forms. Thus, fluctuations in drug effects are minimized and concentration dependent adverse effects that are associated with peak concentrations can be prevented. This feature is of special importance for drugs with a narrow therapeutic index.

CONCLUSION

Based on the previous studies reported, it may be concluded that gastro retentive drug delivery recommends various potential advantages for drugs with poor bioavailability as their absorption is restricted to the upper GI tract. Moreover, they can be delivered efficiently thereby capitalizing on their absorpti on and enhancing absolute bioavailability. In addition, the identification of new diseases and the resistance shown towards the existing drugs considered the need for the introducing new therapeutic molecules. In response, wide arrays of chemical entities have been introduced that have absorption all over the GI tract and. The drugs that are requisite for showing local action in absorption sites require a specialized delivery system which has been achieved by FDDS. Numerous FDDS approaches have been developed such as single and multiple unit HBS, single and multiple unit gas generating systems, hollow microspheres and raft forming systems. All these gastroretentive drug delivery systems are interesting and presenting their own advantages and disadvantages due to which a lot of work is in a row to develop different types of gastroretentive delivery systems of various drugs. Moreover, further studies are expected in the future that would ultimately lead to improved efficiencies of various types of pharmacotherapies.

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